Cetuximab (Erbitux)

Sponsor: ImClone

Review Office: CBER, OTRR

October 10, 2002

Cetuximab (Erbitux)

- Monoclonal antibody therapy.
- Has potential to be an effective therapy for patients with colon cancer.

Review Staff

- Product
  - Dr. Chana Fuchs
  - Dr. Kathryn Stein, Division Director
- Pharmacology and Toxicology
  - Ms. Mercedes Serabian
  - Dr. M. David Green, Branch Chief
- Clinical
  - Dr. Lee Pai-Scherf
  - Dr. Susan Jerian
  - Dr. George Mills, Branch Chief
  - Dr. Patricia Keegan, Deputy Div. Director

Documented Communication
(July 2000 to June 13, 2002)

- 7 face-to-face meetings
- 14 letters
- 52 telephone conversations and meetings
- Total = 73 substantive communications with the sponsor

(slide revised October 18, 2002)

Study 9923

- Metastatic colon cancer patients previously treated with 5FU and irinotecan.
- Enrolled patients previously treated with irinotecan and who had stable disease or progressed at some point during or after irinotecan therapy.
- Treated with cetuximab plus irinotecan.

Study 9923

- Exploratory Phase 2 study in broad group of patients.
- Not intended to support licensure.
- ImClone came to CBER after the study was well underway to ask if the data could support licensure.

Questions About This Approach

- Why was Study 9923 not reviewed as a Special Protocol Assessment (SPA)?
- Why was a single arm study felt to be acceptable?
- Why was ImClone allowed to proceed toward a license application for cetuximab?

SPA

- SPA = Special Protocol Assessment
- Serves as a “contract” between the sponsor and the Agency regarding the design of a trial intended to support licensure.
- Does not apply to studies already underway.
- Cannot be applied retrospectively.
- SPA would not have helped with Study 9923.

Single Arm Studies

- Patients with no other treatment options (general and widely accepted knowledge of expected outcome is the control).
- Well conducted
- Might support an accelerated approval, and sometimes full approval, (e.g. Rituxan, Gleevec).
- Subsets of the original study might be acceptable (e.g. Mylotarg).

Accelerated Approval

- Serious and Life-Threatening Diseases.
- Unmet medical need.
- Requires confirmatory study be completed and supportive to retain license and gain full approval.

License Application

- There are different paths to approval.
- CBER provided advice regarding ImClone's approach.
- CBER recommended other options.
- Sponsor was informed when they chose an approach that would be more rapid, but higher risk.

August 2000 Meeting: ImClone's question

- **Will a subset of the data from the 9923 study be sufficient for an accelerated approval of cetuximab in combination with chemotherapy (irinotecan)?**

August 2000 Meeting: CBER's response

- If you can demonstrate, from existing preclinical and clinical data, that cetuximab as a single agent is not active and that the addition of toxic chemotherapy (e.g. irinotecan, Saltz) is necessary…
- If you can prove that patients had progressive disease on the prior irinotecan therapy …
- If you can provide data to demonstrate tumor response…

CBER Response (cont.)

- If there are enough patients enrolled on study who would fit a strict definition of “refractory to irinotecan” consistent with that used in CDER…
- If you can provide evidence that adequate doses of irinotecan were administered with prior therapy…
- If you can provide data to support the cetuximab dose and schedule selected…
- If the study was conducted well…

ImClone Claim

- ImClone claimed that cetuximab alone would not be effective.
- ImClone took the position that it would be unethical to study single agent cetuximab.
- CBER asked them to provide data to support this claim.

Sept. – Dec. 2000

- We received only part of the information requested at the August 2000 meeting and all issues still remained unresolved.
- We received a request for Fast Track designation.

Fast Track Request

- For use in combination with irinotecan in patients with refractory colorectal cancer.
- We granted Fast Track based upon:
  - Demonstrated potential for benefit
  - Addresses unmet medical need
  - Entire development program included randomized 1st line study
  - Intended to treat a serious and life-threatening disease

Fast Track Designation January 2001

"…cetuximab in combination with irinotecan for its effect on durable tumor responses…in patients with metastatic colon cancer who are refractory to standard chemotherapy [5FU and irinotecan], where refractory is defined as progressive disease during at least two cycles of standard doses of [5FU] and irinotecan."

Advice Letter and Telecon January 2001

- Data submitted to date did not address our original questions.
- We recommended the option of conducting a randomized study to support licensure.
- If randomized study is not done, then they must focus on fulfilling a number of required criteria to enable them to have a successful license application.

Jan 2001 Advice Letter

- **Prove that the response rate to single agent cetuximab did not "overlap" with that seen to cetuximab plus irinotecan.**
  - **Show that cetuximab alone would not be able to result in a comparable response rate.**
  - **Show that irinotecan and its associated toxicity is necessary.**

Jan 2001 Advice Letter

- **If a single arm study of cetuximab alone does not demonstrate this, you should perform a randomized study comparing cetuximab to cetuximab plus chemotherapy.**

Jan 2001 Advice Letter

- **Provide data demonstrating that patients treated with two cycles of irinotecan do no benefit from continued therapy with irinotecan.**
  - **Show us that the cetuximab is necessary to shrink tumors.**
  - **Show us that irinotecan would not achieve these responses on its own.**

Jan 2001 Advice Letter

- **Confirmatory randomized trial should be underway at the time the license application is submitted.**

Jan 2001 Advice Letter

- Provide information on the pathology test (EGFR assay) used to identify patients with EGFR expression.
- Provide analysis of level of EGFR expression correlated with tumor response.

Jan 2001 Advice Letter

- **Provide data to support selected dose and schedule of administration.**

March 2001

- Meeting to discuss their plans for a BLA submission.
- We will need to have data from the single agent study and pilot study of cetuximab plus Saltz regimen.
- Still awaiting pharmacologic data to support selected dose and schedule requested last year.

March to October 2001

- FDA committed to working with sponsor to maximize possibility of a successful application.
- Multiple telephone conferences and additional meetings to discuss specifics of data submission.
  - What is expected
  - What format to use
  - Scope of submission
  - Timeline for submission

June 2001

- Product data submitted as first section of rolling license application.
- Product review completed prior to December filing date.
  - Included 2 week inspection of manufacturing facility.
  - Accelerated schedule.
  - There were no license application filing problems for the product manufacturing.

October 2001

- Clinical data from study 9923 and single agent study submitted.
- Sponsor did not inform us about the randomized study of cetuximab being conducted in Europe by MerckKGA.
  - This is the type of study we had previously asked them to conduct to show the utility of needing toxic chemotherapy.

Cetuximab BLA

- Did not address issues raised in communications of 8/00, 01/01, and 03/01.
- Extensive discrepancies across data sets, missing information, and incorrect information.
- Incomplete safety database.

Is irinotecan necessary?

- Response rates claimed in the combination study and single agent study have overlapping confidence intervals.
- Conclusion: We don’t know if irinotecan and its associated toxicities is necessary to benefit patients.

Is the dose effective?

- The application did not contain data to justify the selected dose and schedule.
- Tumor saturation data that the sponsor previously claimed they had was not provided.

Could the response be due to irinotecan alone?

- The data did not prove that the patients enrolled on the study were “refractory” to irinotecan.
- This definition of refractory was part of the Fast Track designation.
- We don’t know if irinotecan given without cetuximab might have produced the same response.

Are there enough patients?

- There were numerous protocol deviations.
- Not enough patients remained to constitute a sufficiently robust data set.
- Unable to draw conclusions about effectiveness.

Were tumor responses documented?

- Inadequate and inconsistent documentation of radiologists' assessments.
  - Both for individual films and for final consensus
- There were two different tumor response assessment manuals that were not consistent.
- Incorrectly reported measurements for half the data.

Is the safety database complete?

- Incomplete information on deaths and drop outs.
- Inconsistencies and discrepancies between case report forms and data sets.

December 2001

- **Refuse to file (RTF) letter issued.**
  - **This is a very serious decision.**
  - **Multiple internal discussions at all reviewer and supervisory levels.**
  - **Numerous reasons for the RTF.**

Communication with Sponsor

- Policy on communication of RTF
  - CBER staff followed FDA policy
  - Subject of Congressional hearing today

Where do we go from here?

- Continue to work with ImClone to design studies that will provide scientific information for achieving approval.
- Emphasize to ImClone the need for well conducted studies and for focus on FDA requests and advice.
- Support ImClone if they choose to pursue expanded access program.

Cetuximab (Erbitux)

- Has potential to be an effective therapy for patients with colon cancer.
- FDA continues to be committed to dedicating the resources and expertise to support this product through the regulatory process.